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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Ketamine-anesthetized Sprague-Dawley rats were exposed in both E and H orientations of far-field 2.45-GHz continuous-wave radiofrequency radiation (RFR) at a power density of 60 mW/cm ² (whole-body average specific absorption rate of 14 W/kg). Intermittent exposures were performed in both orientations in the same animal to repeatedly increase colonic temperature from 38.5 to 39.5 °C. Tympanic, subcutaneous (sides toward and away from RFR source), and colonic temperature, ECG, arterial blood pressure, and respiratory rate were continuously recorded. Results suggest that, when interpreting results of RFR exposure, animal orientation during irradiation must be considered.				
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Thermal and physiological responses of rats exposed to 2.45-GHz radiofrequency radiation: a comparison of E and H orientation

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Summary. Ketamine-anesthetized Sprague-Dawley rats were exposed in both E and H orientations to far-field 2.45-GHz continuous-wave radiofrequency radiation (RFR) at a power density of 60 mW cm² (whole-body average specific absorption rate of ~14 W/kg). Intermittent exposures were performed in both orientations in the same animal to repeatedly increase colonic temperature from 38.5 to 39.5° C. Tympanic, subcutaneous (sides toward and away from RFR source), and colonic temperature, ECG, arterial blood pressure, and respiratory rate were continuously recorded. The pattern of heat distribution within the animal and the physiological responses were significantly different between E- and H-orientation exposure. Irradiation in E orientation resulted in greater peripheral and tympanic heating, while irradiation in H orientation resulted in greater core heating. Heart rate and blood pressure increased significantly during irradiation and returned to baseline levels when exposure was discontinued; the increases were significantly greater in E than in H orientation. Respiratory rate increased significantly during irradiation in H, but not in E orientation. The physiological responses could have been influenced by the different levels or rates of subcutaneous and tympanic heating, or the differential between core and peripheral heating during E- and H-orientation irradiation. These results suggest that, when interpreting results of RFR exposure, animal orientation during irradiation must be considered.

Introduction

Meaningful evaluation of the biological effects of radiofrequency radiation (RFR) depends on quantitative determination of radiation exposure levels, in order to establish accurate relationships between experimental results and absorbed energy. Using whole-body average specific absorption rate (SAR) as a standard for expressing the amount of energy absorbed has provided some uniformity to experimentation in this field. However, *average*

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SAR provides little information concerning absorbed energy distribution within irradiated animals. Since physiological and behavioral responses are highly temperature dependent, the internal temperature distribution (the *local* SAR) should be known in order to properly evaluate the effects of RFR exposure.

The local and whole-body average energy absorbed by biological tissues varies with a great number of factors, such as carrier frequency, power density, physical dimensions of the organism, and orientation of the subject with respect to the electric and magnetic fields. With respect to the latter factor, several studies (Gandhi 1974; Allen et al. 1976; Merritt et al. 1977; Durney et al. 1980; Lotz 1985; Chou et al. 1985; McRee and Davis 1987) have shown that at equivalent average power densities, E-orientation irradiation (long axis of body parallel to electric field) results in higher whole-body average SARs than does H-orientation exposure (long axis parallel to magnetic field), at least under certain exposure conditions.

Investigations by Chou et al. (1985), D'Andrea et al. (1985), and McRee and Davis (1987) showed that orientation during RFR exposure influenced the local SARs in rat carcasses. However, little is known concerning the effects of orientation on patterns of heat distribution (local SARs) in *living* animals, or how patterns of heat distribution affect behavioral and physiological responses in irradiated animals.

The present study was designed to compare the effects of acute whole-body exposure to 2.45-GHz RFR in E and H orientation upon the patterns of heat distribution (local SARs), the overall heating and cooling responses, and changes in cardiovascular and respiratory function in ketamine-anesthetized rats. This is the first study to investigate possible orientation effects upon cardiovascular and respiratory changes in a living animal exposed to RFR. The carrier frequency of 2.45 GHz was chosen for this study because it is frequently used in RFR bioeffects studies. The anesthetized rat model was chosen for this study because this model allows convenient and reliable acquisition of physiological data, and because preliminary exposures of rats at 2.45 GHz in E orientation produced extremely high subcutaneous temperatures which would likely be painful to unanesthetized animals.

Methods

Animals

Twelve male Sprague-Dawley rats (Charles River Laboratories), weighing between 261 and 319 g (mean \pm SEM, 288 ± 5 g) were used in this study. Animals were housed in polycarbonate cages with free access to food and water, and maintained on a 12 h/12 h, light/dark cycle (lights on at 0600) in a climatically controlled environment (ambient temperature of $24 \pm 1^\circ$ C). Before surgery, animals were fasted for 18 h (water ad libitum). An aortic cannula was installed via the left carotid artery to measure arterial pressure. Ketamine HCl (Vetalar), 150 mg/kg I.M., was administered as the anesthetic, with supplemental doses provided as necessary during experimentation.

Administration of ketamine at approximately this dose has been shown to provide adequate prolonged anesthesia in Sprague-Dawley rats (Smith et al. 1980), and produces a stable animal preparation compatible with physiological monitoring (Jauchem et al. 1984a, b; Frei et al. 1988, 1989).

Immediately after surgery, the animal was placed on a holder in the RFR exposure chamber. The holder consisted of seven 0.5-cm (O.D.) Plexiglas rods mounted in a semi-circular pattern on 4 × 6 cm Plexiglas plates. The animal was instrumented to continuously monitor and record the ECG, mean arterial blood pressure, and respiratory rate, as described previously (Jauchem et al. 1984a, b). Temperature was monitored at four sites: left subcutaneous (SC) (lateral, mid-thoracic, side facing the antenna); right SC (lateral, mid-thoracic, side away from RFR source); right tympanic; and colonic (5–6 cm post-anus). The non-RFR-perturbing thermistor probes were attached to a BSD-200 precision thermometry system (BSD Medical Corporation) to obtain continuous (12-s sampling intervals) temperature readings.

RFR equipment

The continuous-wave RFR fields were generated by a model 1325 RF power source (Coher Electronics, Inc., Stamford, CT, USA), and were transmitted by a model 644 standard-gain horn antenna (Narda Microwave Corporation, Hauppawge, NY, USA). Irradiation was performed under far-field conditions (animal positioned on boresight 115 cm from antenna), and the incident power density of the field was determined with an electromagnetic radiation monitor (model 8616 (Narda Microwave Corporation, Hauppawge, NY, USA) employing a model 8623 probe). The field distribution was measured over a 40 cm horizontal distance (20 cm both sides of boresight). The field was found to be virtually constant in E orientation (< 1% variation) and varied < 10% in H orientation. During exposures, generator power output was monitored continuously with a model 432-B power meter (Hewlett-Packard), and was recorded on a Gould 2600S recorder. Irradiation was performed in an Eccosorb RF-shielded anechoic chamber (Rantec, Emerson Electric Co., Calabasas, CA, USA) at Brooks Air Force Base, Texas, USA. The chamber temperature ($27 \pm 0.5^\circ\text{C}$) and relative humidity ($20 \pm 5\%$) were monitored during experimentation.

Exposure conditions

Animals were exposed individually in both the E and H orientation (left lateral exposure, long axis parallel to electric or magnetic field) to 2.45-GHz RFR at a boresight power density of 60 mW/cm^2 (SARs of 14.5 ± 2.2 and $12.4 \pm 2.6\text{ W/kg}$ for E and H, respectively). Normalized SARs, determined calorimetrically according to the methods of Allen and Hurt (1979) and Padilla and Bixby (1986) on eleven animal carcasses, were 0.24 and 0.21 ($\text{W/kg}/(\text{mW/cm}^2)$), for E and H, respectively. These values are not significantly different.

A stable regimen of colonic temperature (T_c) change was used for com-

paring the effects of irradiation in E and H orientation. After initial exposure in E or H orientation had increased T_c to 39.5° C, irradiation was discontinued. When T_c returned to 38.5° C, irradiation was initiated until T_c again increased to 39.5° C. This procedure was repeated for three cycles. The antenna was then rotated, and three additional cycles were completed in the second orientation. The orientation in which the animals were first exposed was alternated daily. After irradiation in both orientations, the animals were euthanized, and the carcasses were then exposed to RFP in E or H orientation for 12–15 min.

Irradiation of live animals produces localized heating; however, localized temperature increases are not related solely to the absorption of RF energy. Heating or cooling related to blood flow, changes in metabolic activity, and heat transfer to the environment must also be considered. In this paper, live animal heating rates are termed SHRs (specific heating rates, W/kg), and carcass heating rates are termed SARs.

The term "local SAR", as used in numerous recent investigations (Chou et al. 1985; D'Andrea et al. 1985, 1987; McRee and Davis 1987) refers to the calculated SAR based upon a temperature increase at a specific monitoring site, such as the colon. Although the probe measures the temperature of a very small area of tissue (essentially the point in contact with the probe), the local SAR is expressed in terms of W/kg.

The following differential equations, which closely model the temperature changes in the present experiments, rely on Newton's law of cooling (where the rate of heat loss is proportional to the temperature difference between the sample and its environment). Accordingly, as the sample's temperature begins to increase, heat loss begins almost immediately. Equations (1) and (2) were derived from similar equations presented by McRee (1974). Equation (3) is from Johnson (1975).

$$dH(t)/dt = K - n[H(t) - A] = \text{Rate of heating}, \quad (1)$$

$$dC(t')/dt' = -n[C(t') - A] = \text{Rate of cooling}, \quad (2)$$

$$\text{SAR or SHR} = 4186(S)K, \quad (3)$$

where

$H(t)$ = the temperature of the sample during irradiation with respect to time t .

$C(t')$ = the temperature of the sample after irradiation with respect to time t' .

A = the temperature of the sample's environment, usually air, kept at a constant temperature.

K = the rate of heating due to RF energy or energy from other sources, usually constant.

n = the Newtonian cooling constant or, more appropriately, the heat loss constant.

S = the specific heat of the sample, 0.824 cal/gm° C for our study.

Time is in seconds, temperature is in degrees C, and the prefix d denotes a differential. For determining the SARs or SHRs, points were chosen on

the heating curve and matched with points on the cooling curve that were at the same temperature. Subtracting the cooling rate from the heating rate at the selected points results in the cancellation of the heat loss rate. Given two points in time, t_1 and t_2 , where $H(t_1) = C(t_2)$, then:

$$dH(t_1)/dt - dC(t_2)/dt' = K - n[H(t_1) - A] + n[C(t_2) - A] = K. \quad (4)$$

Hence,

$$\text{SAR or SHR} = 4186(0.824)[dH(t_1)/dt - dC(t_2)/dt'] \text{ in W/kg.} \quad (5)$$

Software, similar to that written by Lozano and Hurt (1984), has been written for the BSD-200 computer, which calculates average localized SARs and SHRs after the temperature data has been recorded on disk.

Statistics

Data obtained from repeated cycles in the two exposure orientations were averaged for each animal and are expressed as group means \pm SEM. Student's t -test for paired data (two-tailed) was used to determine if significant differences existed between values obtained in E and H orientation. For heart rate (HR), mean arterial blood pressure (BP), and respiratory rate (RR) data, analyses were performed on changes between T_c of 38.5 and 39.5°C, rather than on absolute values. Student's t -test for unpaired data was used to determine if significant differences existed in the localized SARs in the E- and H-orientation irradiated carcasses. P values of less than 0.05 were considered to indicate significance in all tests.

Results

Thermal changes

Summarized in Table 1 are the respective times for T_c to increase from 38.5 to 39.5°C in E and H orientations, and to return to 38.5°C. Table 2 shows the right and left SC and tympanic temperature increases that accompanied the 1°C T_c increase. The times to accomplish and to recover from a 1°C T_c increase were virtually equal for E- and H-orientation exposures. The SC temperature increase on the side facing the RFR source (left side)

Table 1. Colonic temperature (T_c) changes (mean \pm SEM) in rats ($n = 12$) exposed in E and H orientation to 2.45-GHz CW radiofrequency radiation

Exposure condition	t_r (min) ^a	t_d (min) ^b
E orientation	8.6 \pm 0.4	16.6 \pm 1.3
H orientation	8.0 \pm 0.2	15.2 \pm 1.1

^a t_r = time to achieve a 1°C T_c increase

^b t_d = time to recover to initial temperature after irradiation

Table 2. Local temperature increase (mean \pm SEM) that accompanied a 1°C colonic temperature increase in rats ($n=12$) exposed to 2.45-GHz CW RFR in E and H orientation

Temperature monitoring site	Temperature increase (°C)	
	E orientation	H orientation
Left subcutaneous ^a	4.7 \pm 1.0	2.0 \pm 0.2*
Right subcutaneous ^b	0.5 \pm 0.04	0.9 \pm 0.1*
Tympanic	1.5 \pm 0.06	1.2 \pm 0.03*

^a Side toward RFR source

^b Side away from RFR source

* Significant difference ($p < 0.05$) between E and H values

Table 3. Localized SARs (mean \pm SEM) in rat carcasses exposed to 2.45-GHz CW RFR in E or H orientation

Monitoring site	Localized SAR (W/kg)	
	E orientation ($n=7$)	H orientation ($n=5$)
Colonic	4.3 \pm 1.3	10.8 \pm 0.5*
Tympanic	12.7 \pm 3.4	15.2 \pm 1.2
Right subcutaneous ^a	3.1 \pm 0.8	7.5 \pm 0.8*
Left subcutaneous ^b	55.6 \pm 10.4	29.7 \pm 5.4*

^a Side away from RFR source

^b Side toward RFR source

* Significant difference ($p < 0.05$) between E and H values

was significantly greater in E than in H orientation. The tympanic temperature increase was also significantly greater in E than in H orientation. In contrast, the SC temperature change on the side away from the source (right side) was significantly less in E than in H orientation.

After irradiation in E and H orientation, the rats were euthanized, and the carcasses were immediately irradiated in E ($n=7$) or H ($n=5$) orientation. Shown in Table 3 are the local SARs. The colonic and right SC SARs were significantly less in E than in H orientation. The tympanic SAR was greater in H than in E orientation; however, the difference was not significant. The left SC SAR was significantly greater in E orientation.

Since, in living systems, metabolic heat input and various cooling mechanisms occur concurrently with RFR absorption, SHRs, in addition to SARs, are of interest. Shown in Table 4 are the localized SHRs at four monitoring sites during E- and H-orientation exposure. No significant difference in colonic SHR occurred between E- and H-orientation exposure. All other monitoring sites showed significant differences. The tympanic and left SC SHRs were significantly higher in E than in H orientation, while the right SC SHR was significantly lower in E than in H orientation.

Table 4. Localized specific heating rates (mean \pm SEM) in rats ($n=12$) exposed to 2.45-GHz CW RFR (60 mW/cm²) in E and H orientation

Temperature monitoring site	Localized specific heating rates (W/kg)	
	E orientation	H orientation
Colonic	12.3 \pm 0.5	11.8 \pm 0.4
Tympanic	15.1 \pm 0.6	13.1 \pm 0.3 *
Left subcutaneous ^a	56.6 \pm 9.6	23.7 \pm 3.1 *
Right subcutaneous ^b	6.4 \pm 0.6	10.3 \pm 0.8 *

^a Side toward RFR source

^b Side away from RFR source

* Significant difference ($p < 0.05$) between E and H values

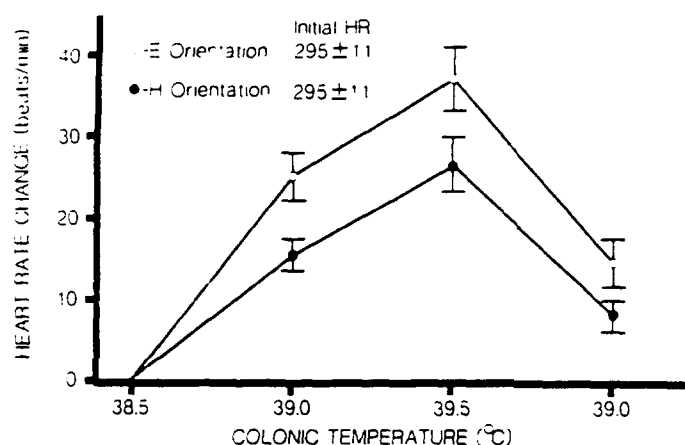


Fig. 1. Heart rate changes in rats during RFR-induced 1°C temperature cycles in E and H orientation ($n=12$). Irradiation was initiated at 38.5°C and discontinued at 39.5°C. The data are normalized to the values obtained at 38.5°C

Physiological responses

The HR changes that accompanied the 1°C T_c cycles are displayed in Fig. 1. In both E and H orientations, HR significantly increased as T_c increased from 38.5 to 39.5°C, and returned to near baseline levels during the recovery periods; the HR changes were significantly greater in E orientation.

Shown in Fig. 2 are the BP changes that occurred during the 1°C T_c cycles. During exposures in both E and H orientation, BP significantly increased during irradiation, and returned to baseline after cessation of irradiation. BP changes during E-orientation exposure were significantly greater than during H-orientation exposure.

The RR changes that occurred during the 1°C T_c cycles are shown in Fig. 3. During exposure in E orientation, RR did not change significantly; however, exposure in H orientation resulted in a significant RR increase.

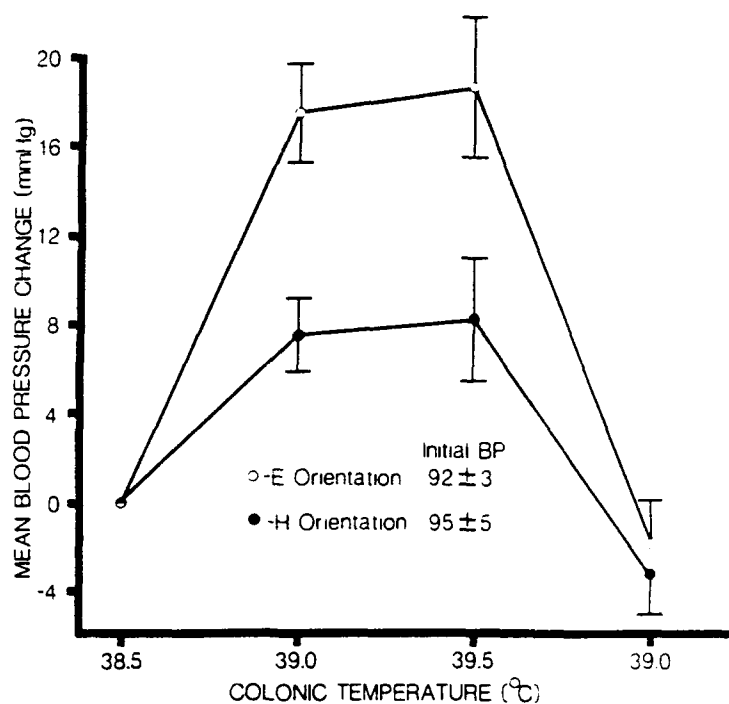


Fig. 2. Mean arterial blood pressure changes in rats during RFR-induced 1°C temperature cycles in E and H orientations ($n=12$). The data are normalized to the values obtained at 38.5°C

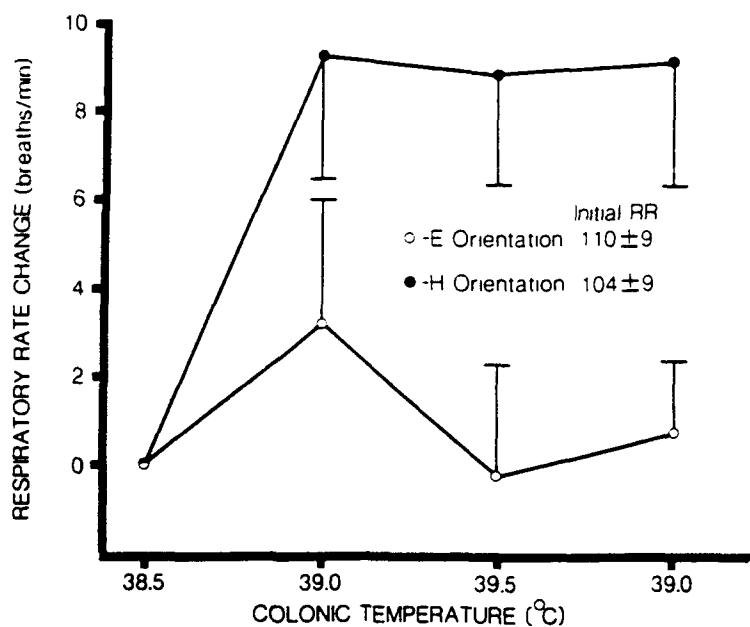


Fig. 3. Respiratory rate changes in rats during RFR-induced 1°C temperature cycles in E and H orientations ($n=12$). The data are normalized to the values obtained at 38.5°C

Discussion

In studies of environmental heating, core-to-skin thermal gradients are usually assumed to be minimal (Simon et al. 1986). During RFR exposures, however, particularly at higher frequencies, relatively large thermal gradients must be taken into account. Evidence suggests that during irradiation at equivalent power densities at certain frequencies, exposure in E orientation results in higher SARs than H-orientation exposure. Results of the present study indicate that even when E- and H-orientation exposures are made at similar SARs, as opposed to equivalent power densities, drastic differences in sites of energy deposition create large thermal gradients within the exposed animal.

The inequality of heat-distribution patterns in live animals exposed to RFR in E and H orientation is of considerable significance. Most RFR-induced bioeffects are regarded as being thermal in nature; however, during the last decade, numerous investigators have categorized noted effects as being "nonthermal" in nature. In some studies, the power levels used during irradiation were extremely low, and were very unlikely to cause a temperature increase. In other studies at higher power levels, effects were considered to be nonthermally induced because the core temperature (usually colonic or rectal) did not appreciably change during irradiation. This latter line of reasoning may be questioned because, depending on exposure conditions, localized areas of the body may experience large temperature changes while the core temperature remains virtually unchanged. For example, Spiegel et al. (1980) found that in human models irradiated with 80-MHz RFR (SAR of 1.4 W/kg) the temperature increase in the thigh area was 3–4°C greater than in the colonic area. D'Andrea et al. (1985) noted, in irradiated rat carcasses, localized hot spots that were significantly higher than whole-body average temperature changes. In an extension of their earlier work, D'Andrea et al. (1987) found that the higher than average local SARs noted in rat carcasses were reflected in localized hot spots in ketamine-anesthetized rats. Frei et al. (1988) showed an unequal heating pattern in anesthetized rats exposed to 2.8-GHz RFR (SAR of 8–20 W/kg) in H orientation: SC and tympanic heating was significantly greater than colonic heating.

In the present study, irradiation in H orientation produced a more uniform pattern of heat distribution in the rat than did E-orientation exposure (Table 2). Comparison between live animal (Table 4) and carcass (Table 3) exposure suggests that the T_c increase during E-orientation irradiation of live animals was due in great part to heat transfer from periphery to core via the circulatory system. Conversely, the SC temperature increase seen in H orientation may have been partially due to heat transfer from core to periphery. Results of this study indicate that animal orientation during irradiation *must* be considered in interpretation of results of RFR exposure. It is possible that some previous reports of nonthermally-induced RFR bioeffects were influenced by undetected orientation-specific localized hotspots, particularly in anesthetized or restrained animals.

The present study showed that several physiological parameters were

influenced by the heat-distribution pattern. The HR increase was significantly greater during irradiation in E than in H orientation (Fig. 1). Although the exact mechanism responsible for the greater HR increase during E-orientation exposure is unclear, it is probable that the difference was primarily related to the level or rate of peripheral heating. This topic was discussed in a recent article (Frei et al. 1989) concerning exposure of rats to 9.3-GHz RFR (H orientation) in which levels of SC temperature increase closely resembled the present 2.45-GHz E-orientation-induced increase. The higher SC temperature, or the faster rate of SC temperature increase during E-orientation exposure, may have influenced the level of stress hormone release (epinephrine, norepinephrine, corticosterone), which is known to enhance cardiovascular function. Lotz (1985) exposed rhesus monkeys to 225-MHz RFR in E and H orientation and found that corticosterone release was significantly greater during E-orientation exposure.

Adair (1977) and Adair et al. (1984) have shown that minor changes ($<0.1^{\circ}\text{C}$) in hypothalamic temperature can influence thermoregulatory response in the whole animal. Although we did not directly measure hypothalamic temperature, tympanic temperature has been shown to be a reliable indicator of hypothalamic temperature in humans (Benzinger and Taylor 1963), and of brain temperature in rats (Robinson et al. 1967; Dunscombe et al. 1980). We obtained a small ($<0.3^{\circ}\text{C}$), but consistently higher tympanic temperature change in E orientation than in H orientation. This difference may have contributed significantly to the heightened cardiovascular response seen during exposure in E orientation.

Previous studies of human cardiovascular responses to hyperthermia have revealed an increase in HR accompanied by a decrease in BP (Kim et al. 1979; Tonnesen et al. 1987). The BP decrease was attributed primarily to cutaneous vasodilation and increased skin blood flow, an effect also noted by Phillips et al. (1975) and Adair and Adams (1980) during RFR exposure in which the T_{c} increased only slightly. In our experiments, however, BP increased significantly (Fig. 2), and the increase in E orientation was significantly greater than in H orientation. Pettigrew et al. (1974) also reported a rise in BP during hyperthermia in humans, and Cooper et al. (1962) noted hypertension in rats exposed to RFR. In these and the present study, local skin vasodilation may have been counteracted by other cardiovascular adjustments, such as increased cardiac output due to increased HR (Gorman and Proppe 1984).

In the present study, RR significantly increased during irradiation in the H orientation, but not in the E orientation (Fig. 3). Irradiation of carcasses showed that the major site of energy deposition in H orientation occurred in the animal core. Activation of deep receptors during irradiation in H orientation may have influenced respiratory rate to a greater degree than peripheral receptor activation in E orientation. Simon (1974) has suggested that activation of deep thermal receptors can play an important role in stimulation of respiration.

In summary, our results showed significant differences between the effects of E- and H-orientation exposure to RFR (2.45 GHz, 60 mW/cm²,

CW) upon the pattern of heat distribution in ketamine-anesthetized rats and rat carcasses. These differences were also reflected in the animals' HR, BP, and RR changes during irradiation. During RFR exposure that increased colonic temperature from 38.5 to 39.5°C, the SC temperature increase on the side nearest the RFR source, and the tympanic temperature increase, were both significantly greater in E than in H orientation; the opposite was true for the SC temperature away from the source. HR and BP increased significantly during irradiation, and returned to baseline levels when exposure was discontinued; the increases were significantly greater in E than in H orientation. RR increased significantly during irradiation in H but not in E orientation. Although the physical and biological mechanisms are unclear at this time, at the commonly used frequency of 2.45 GHz there is a tremendous difference in sites of energy deposition between E and H orientation; this difference significantly affects the rat's responses to RFR exposure. Additional studies are needed to determine if these responses also occur at other frequencies and power levels.

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